IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 19-2017 (RGA) (SRF)
	)	**CONSOLIDATED**
MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

EXELIXIS' ANSWERING POST-TRIAL BRIEF
ON THE VALIDITY OF THE '473 PATENT

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TABLE OF ABBREVIATIONS

Abbreviation	Description
’473 patent	U.S. Patent No. 7,579,473 (JTX-3)
’776 patent	U.S. Patent No. 8,877,776 (JTX-1)
ANDA	Abbreviated New Drug Application
Asserted Claims	For the ’473 patent, claim 5 For the ’776 patent, claim 1
FDA	United States Food and Drug Administration
Exelixis	Exelixis, Inc.
MSN	MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.
Tr.	Final Trial Transcripts
UF	Uncontested Facts (D.I. 270, Ex. 1)
POSA	Person of ordinary skill in the art. For the ’473 patent, a POSA would have the characteristics described at UF ¶ 23 as of September 26, 2003; for the ’776 Patent, a POSA would have the characteristics described at UF ¶ 46 as of January 15, 2010.
CoC	Certificate of Correction
MSN Br.	MSN’s Opening Post-Trial Brief on Invalidity (D.I. 307)
EOFOF	Exelixis’ Opening Proposed Findings of Fact (D.I. 309)
MOFOF	MSN’s Opening Proposed Findings of Fact (D.I. 306)
EAFOF	Exelixis’ Answering Proposed Findings of Fact
RCC	Renal Cell Carcinoma
HCC	Hepatocellular Carcinoma
DTC	Differentiated Thyroid Cancer
VEGFR	Vascular Endothelial Growth Factor Receptor
EGFR	Epidermal Growth Factor Receptor

TKI	Tyrosine Kinase Inhibitor
Kirin	WO 03/000660 A1, *Quinoline Derivative and Quinazoline Derivative Inhibiting Self-Phosphorylation of Hepatocytus Proliferator Receptor, and Medicinal Composition Containing the Same* (DTX-6 (Japanese) or DTX-7 (English translation))
Traxler	Peter Traxler, *Tyrosine Kinases as Targets in Cancer Therapy – Successes and Failures*, 7 Expert Op., Therapeutic Targets 215 (2003) (DTX-17)
Maulik	Gautam Maulik et al., *Role of the Hepatocyte Growth Factor Receptor, c-Met, in Oncogenesis and Potential for Therapeutic Inhibition*, 13 Cytokine & Growth Factor Reviews 41 (2002) (DTX-37)
Shawver	Laura K. Shawver et al., *Smart Drugs: Tyrosine Kinase Inhibitors in Cancer Therapy*, 1 Cancer Cell 117 (2002) (DTX-39)
Onderwater 1998	Rob C.A. Onderwater et al., *Cytotoxicity of a Series of Mono- and Di-substituted Thiourea in Freshly Isolated Rat Hepatocytes: A Preliminary Structure-Toxicity Relationship Study*, 125 Toxicology 117 (1998) (DTX-18)
Salaün	J. Salaün, *Cyclopropane Derivatives and their Diverse Biological Activities*, 207 Topics in Current Chemistry 1 (2000) (DTX-28)
Fry	D.W. Fry et al., *Specific, Irreversible Inactivation of the Epidermal Growth Factor Receptor and erbB2, By a New Class of Tyrosine Kinase Inhibitor,* 95 Proc. Nat'l Acad. Sci. USA 12022 (1998) (DTX-30)
NCCN Guidelines	NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer Version 3.2022 – Nov. 4, 2021 (PTX-648)
Kelner	M. Kelner et al., *Efficacy of Acylfulvene Illudin Analogues Against a Metastatic Lung Carcinoma MV522 Xenograft Nonresponsive to Traditional Anticancer Agents: Retention of Activity Against Various mdr Phenotypes and Unusual Cytotoxicity Against ERCC2 and ERCC3 DNA Helicase-deficient Cells*, 55 Cancer Res. 136 (1995) (DTX-27)
McMorris	T. McMorris et al., *Structure and Reactivity of Illudins*, 45 Tetrahedron 5433 (1989) (DTX-25)

I. INTRODUCTION

Cabozantinib, the active ingredient in Exelixis' CABOMETYX® product, has benefited thousands of patients suffering from kidney cancer, hepatocellular carcinoma, and thyroid cancer. In clinical trials, CABOMETYX® has been shown to slow disease progression and prolong patient survival even when other treatments have failed. The clinical success of CABOMETYX® is directly attributable to cabozantinib, a tyrosine kinase inhibitor ("TKI") that targets not only c-Met but at least twelve other tyrosine kinases. As Exelixis' expert clinician Dr. Daniel George testified at trial, the unique inhibition profile of cabozantinib is the "secret sauce" responsible for the clinical success of CABOMETYX®. Tr. 579:21-580:2 (George); EAFOF ¶ 53.

Discovered in September 2003, cabozantinib is claimed in U.S. Patent No. 7,579,473 (the "'473 patent"). MSN does not dispute that its proposed generic version of CABOMETYX® infringes claim 5 of the '473 patent. It asserts that cabozantinib would have been obvious in view of the prior art. But there was nothing obvious about a novel, small-molecule c-Met inhibitor discovered at a time when targeted cancer therapy was in its infancy and failed attempts at new cancer treatments were common. While some approaches to targeted therapy had been validated in the clinic, c-Met was uncharted territory. The structure of the c-Met tyrosine kinase was unknown. Preclinical models proven effective for evaluation of c-Met inhibitors did not exist. And not a single c-Met inhibitor of any kind had been tested in the clinic. Moreover, researchers would have been faced with exploring a variety of potential approaches for c-Met inhibition, of which a small molecule c-Met inhibitor was just one.

Given the many choices a skilled artisan would have had to make to discover cabozantinib, MSN cannot meet its burden to show invalidity by clear and convincing evidence. The selection of tyrosine kinase inhibition as opposed to other targeted cancer treatments was not obvious. The selection of c-Met as a target was not obvious given the absence of information about it as

compared to other tyrosine kinases. The decision to develop a small molecule inhibitor, instead of pursuing alternatives such as antibodies, was not obvious. And the selection of Example 5 from the Kirin reference and the modification of it with a cyclopropyl group at one specific location (as opposed to the many other potential substituents and various other locations on Example 5) was not obvious.

MSN's obviousness case is thus riddled with impermissible hindsight at every step. Only hindsight can explain MSN's focus on a small molecule c-Met inhibitor given the array of other options available to a skilled artisan in September 2003. Only hindsight can explain MSN's zeroing in on the Kirin reference, a patent application that exemplifies 333 small molecules that inhibited c-Met but does not contain clinical data or clinical validation for a single one. Only hindsight can explain MSN's selection of Kirin Example 5, a malonamide[1], as a "lead compound," when not a single malonamide was included in Kirin's list of five "most preferred" compounds, and the Kirin inventors did not report any in vivo pharmacological testing for any malonamide compound. Only hindsight can explain MSN's categorical disregard of Kirin's thiourea, urea and amide compounds, including five that were identified as "most preferred" and 23 that were tested in vivo. And only hindsight can explain MSN's assertion that an ordinarily skilled artisan would have been motivated to add a cyclopropyl group (as opposed to one of the many other potential substituents) to Example 5, let alone at the precise location that results in cabozantinib. Moreover, MSN barely addresses its burden to show that a skilled artisan would have had a reasonable expectation of success. As Exelixis' chemistry expert Dr. David MacMillan explained, the impact of changes made to a chemical structure is unpredictable as a general matter, and the

[1] A malonamide is a chemical group that contains a carbonyl next to a nitrogen, another carbonyl next to a nitrogen, and a carbon in between. EAFOF ¶ 23 n.3; *see infra* § II.B.

unpredictability would have been particularly acute given the limited knowledge of the c-Met tyrosine kinase and its binding site in September 2003. An ordinarily skilled artisan would have had substantial concerns that the modification proposed by MSN would result in a compound that would not inhibit c-Met, and might also be toxic.

MSN's challenge to the validity of the '473 patent should be rejected.

II. THE '473 PATENT AND CABOZANTINIB

A. Asserted Claim 5

Claim 5 is the only claim of the '473 patent asserted against MSN. Claim 5 is directed to the compound cabozantinib or a pharmaceutically acceptable salt of cabozantinib. UF ¶ 19; EAFOF ¶ 12. MSN has stipulated to infringement of claim 5. UF ¶ 20. The only issue the parties addressed at trial for claim 5 of the '473 patent was alleged invalidity based on obviousness. D.I. 275 [Redacted Pretrial Order] at ¶¶ 6, 71. The parties have agreed that, for purposes of this case, the priority date for claim 5 is September 26, 2003. UF ¶ 22.

B. Cabozantinib

Cabozantinib is a reversible, spectrum-selective TKI.[2] EAFOF ¶¶ 10, 11. A TKI is a targeted therapy that inhibits specific tyrosine kinase activity.[3] EAFOF ¶ 9. Cabozantinib inhibits the tyrosine kinase activity of c-Met, VEGFR 1, 2 and 3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2. EAFOF ¶ 10; PTX-343 (CABOMETYX® Label) at 28.

The two-dimensional depiction of cabozantinib set forth below shows a malonamide group (in blue), which contains two carbonyl groups (circled in purple). EAFOF ¶ 23 n.3. The

[2] A reversible inhibitor, such as cabozantinib, binds to a target and after a period of time, will be released from the target and removed from the body. EAFOF ¶ 11. A spectrum-selective inhibitor, such as cabozantinib, binds to multiple tyrosine kinases instead of only one. EAFOF ¶ 10.

[3] A tyrosine kinase is an enzyme that activates cellular proteins. EAFOF ¶ 9. Tyrosine kinases have roles in normal cell function, but may also contribute to the growth of cancerous tumors and metastasis. EAFOF ¶ 9.

malonamide group in cabozantinib includes a three-member carbon ring called a cyclopropyl (in red). EAFOF ¶¶ 23 n.3, 44.

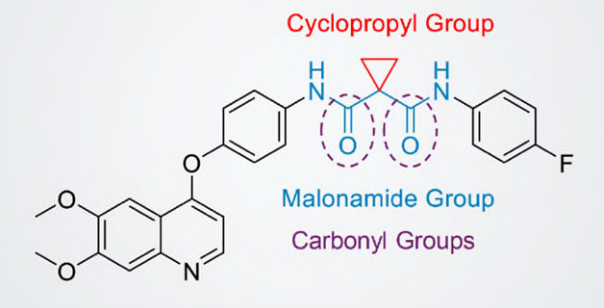

Figure 1 – Two-Dimensional Structure of Cabozantinib (PDX-5.9)

Cabozantinib is the active ingredient in CABOMETYX®, which has been approved to treat renal cell carcinoma ("RCC"), hepatocellular carcinoma ("HCC"), and differentiated thyroid cancer ("DTC"). EAFOF ¶ 8.

III. ARGUMENT

A. A Skilled Artisan Would Not Have Been Motivated to Pursue a c-Met Inhibitor Over Other More Promising Targets in September 2003

In September 2003, improved oncology drugs were desperately needed. EAFOF ¶¶ 14, 55. Existing treatments, such as chemotherapy, surgery, and radiation, had significant shortcomings.[4] EAFOF ¶ 14. Pharmacological targeted cancer therapies provided a new and promising approach. EAFOF ¶ 15. Unlike generalized therapies, targeted therapies could selectively target specific proteins in particular cells. EAFOF ¶ 15.

By September 2003, researchers had identified many different types of targeted therapies to treat cancer; tyrosine kinase inhibition represented just one approach being explored. EAFOF ¶¶ 15, 16. As MSN's clinical expert Dr. Mega admitted, the number of potential targets in 2003

[4] For example, chemotherapy, the most common treatment for cancer in September 2003, kills both cancerous and healthy cells throughout the body and thus results in many undesirable side effects. EAFOF ¶ 14.

was "plentiful." Tr. 802:3-13 (Mega); EAFOF ¶ 15. For example, the Oliff article upon which MSN relies (MSN Br. at 5) identified many types of targeted cancer therapies of which a skilled artisan would have been aware. DTX-66 (Oliff) at 5; EAFOF ¶ 15. And even within the specific approach of tyrosine kinase inhibition, potential targets were numerous. Traxler, another article cited by MSN (MSN Br. at 5-8), identified more than twenty different tyrosine kinase targets that were being evaluated in drug discovery oncology projects. DTX-17 (Traxler) at 1, 3, 11-13; EAFOF ¶ 16.[5]

In September 2003, few examples of successful targeted cancer therapies, let alone TKIs, existed. As Exelixis' clinical expert Dr. George explained, the field was in its "early days." EAFOF ¶ 15. Moreover, in the context of TKIs, researchers knew more about some tyrosine kinases than others. EAFOF ¶¶ 17-19, 21. For example, a skilled artisan would have known that GLEEVEC®, approved to treat leukemia, inhibited Bcr-Abl, c-Kit, and PDFGR. EAFOF ¶ 17. Similarly, a skilled artisan would have known that HERCEPTIN®, approved to treat breast cancer, inhibited ERBB2. EAFOF ¶ 17. Likewise, a skilled artisan would have known that TARCEVA® and IRESSA®, which were in clinical trials for treatment of non-small cell lung cancer, inhibited EGFR. EAFOF ¶ 17. As Dr. George explained, many companies were developing drugs that targeted the EGFR and VEGFR kinases. EAFOF ¶ 17. As of September 2003, an ordinarily skilled artisan would have been motivated to pursue development of TKIs for these and other targets with clinical validation. EAFOF ¶¶ 18, 21.

In contrast, much less was known about the c-Met kinase in September 2003. Unlike more studied tyrosine kinases, such as EGFR and ERBB2, no structural information was available for

[5] Compounding the plentiful number of targets available as of 2003, a skilled artisan would also have had to decide, among other things, whether to pursue a small molecule or a monoclonal antibody. EAFOF ¶¶ 16 n.2, 21.

c-MET. EAFOF ¶ 19. As Dr. George explained, proven pre-clinical models for c-Met did not yet exist. EAFOF ¶ 19. Nor had researchers disclosed any clinical development of a c-Met inhibitor. EAFOF ¶ 19. Indeed, none of the articles upon which MSN relies (*see* MSN Br. at 7-8 (discussing Traxler, Maulik, and Shawver)) identifies any small molecule c-Met inhibitor in clinical development or reports any clinical research on a small molecule c-Met inhibitor. EAFOF ¶ 20. Traxler and Shawver only discussed c-Met TKIs briefly. DTX-17 (Traxler) at 13; DTX-39 (Shawver) at 5; EAFOF ¶ 20. And Maulik did not discuss any small-molecule inhibitors of c-Met, but only referenced other types of inhibitors of the c-Met signaling pathway, such as antibiotics and peptide inhibitors. DTX-37 (Maulik) at 15-16; EAFOF ¶ 20.

Although MSN relies upon Dr. George's agreement in response to a question seeking a "yes or no" answer that there was a motivation to pursue a c-Met inhibitor in September 2003 (MSN Br. at 7), Dr. George made clear that there would have been "no motivation to pursue a c-Met inhibitor compared with other better-known targets at the time" (Tr. 594:3-8 (George); EAFOF ¶ 21). This is because investigating a lesser-known target like c-Met, posed a higher risk of failure as compared to better-known targets. EAFOF ¶ 21. To lower the risk of developing a TKI, an ordinarily skilled artisan would have focused on where "you have the most likelihood of clinical development and clinical success." Tr. 571:3-16 (George); EAFOF ¶ 18. This would have been in areas where skilled artisans had clinical validation that the target may effectively treat the disease. EAFOF ¶ 18. Dr. MacMillan agreed, observing that the focus would have been on the most promising targets and that c-Met was "a long way from there." Tr. 733:23-734:11 (MacMillan); EAFOF ¶ 19. Even Dr. Lepore admitted that positive clinical results "would be in a list of things that one would consider" in determining which treatments to pursue. Tr. 467:10-15 (Lepore); EAFOF ¶ 18.

MSN's suggestion that an ordinarily skilled artisan would have focused specifically on a c-Met inhibitor is thus predicated on "an overly narrow statement of the problem," which can represent a form of prohibited reliance on hindsight.[6] *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (internal quotation marks omitted). Such an approach fails to consider other categories of compounds that an ordinarily skilled artisan "would have been aware of in the relevant time-period," including FDA-approved therapies and compounds that had already demonstrated efficacy in humans. *See Mitsubishi Tanabe Pharma Corp. v. Sandoz, Inc.*, 533 F. Supp. 3d 170, 194-95 (D.N.J. 2021). Moreover, contrary to MSN's suggestion, an ordinarily skilled artisan seeking to develop a drug would have "started by looking at FDA-approved drugs or at compounds with demonstrated clinical efficacy." *UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 542 (D. Del. 2016), *aff'd* 890 F.3d 1313 (Fed Cir. 2018), *cert. denied*, 139 S. Ct. 574 (2018). In sum, given the absence of any positive predictors of clinical success, an ordinarily skilled artisan would not have been motivated to pursue a c-Met inhibitor over other more promising targets.

B. A Skilled Artisan Would Not Have Selected Example 5 of Kirin as a Lead Compound

As MSN admits, the lead compound analysis "'requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds ***over other compounds in the prior art***.'" MSN Br. at 12 (quoting *Daiichi Sankyo Co. v. Matrix Labs.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (emphasis

[6] MSN's reliance on *Pfizer, Inc. v. Apotex, Inc.* (MSN Br. at 9) is misplaced. There, the Federal Circuit limited its holding to "the *particularized facts of this case*," which did not involve the discovery of a new chemical entity. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) (emphasis in original), *cert. denied*, 128 S. Ct. 110 (2007).

added), *cert. denied*, 131 S. Ct. 1678 (2011)). MSN has failed to demonstrate that an ordinarily skilled artisan would have selected Kirin Example 5 as a lead compound.

1. A Skilled Artisan Seeking to Develop a Safe and Effective Targeted Cancer Therapy In September 2003 Would Not Have Started With Kirin

In September 2003, tremendous interest surrounded the development of targeted cancer treatments, but the field was in its early days and substantial uncertainty surrounded the clinical development of tyrosine kinase inhibitors. EAFOF ¶¶ 15, 17. To reduce risk and increase the odds of success, a skilled artisan seeking to develop a new targeted therapy would have gravitated to targets that had already been validated in clinical research. *See supra* § III.A. The Kirin reference that serves as the cornerstone of MSN's obviousness case contains no such proof of concept. Not one of the compounds disclosed in Kirin, let alone MSN's "lead compound" Example 5, was clinically validated. Indeed, Kirin does not include any clinical data for the exemplified c-Met inhibitors, nor does the reference describe any c-Met inhibitor in clinical development. EAFOF ¶ 22. In addition, the only pharmacological data in Kirin pertains to inhibition of c-Met; Kirin does not disclose whether the exemplified compounds inhibit other tyrosine kinases. EAFOF ¶ 22. An ordinarily skilled artisan seeking to develop an effective cancer therapy thus would not have focused on Kirin, which was directed to a single target that had not been clinically validated, as a starting point for further development. EAFOF ¶ 22.

MSN attempts to skirt these deficiencies by asserting that Kirin would have been the starting point for a skilled artisan "motivated to develop a small molecule c-Met inhibitor." MSN Br. at 11. In so doing, MSN runs afoul of the rule that "'[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.'" *Insite*, 783 F.3d at 859-60 (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)). Here, the problem to be solved (without the benefit of hindsight)

was the development of an effective targeted cancer therapy. As both Dr. George and Dr. MacMillan explained, while acknowledging that c-Met had been identified as a potential target, an ordinarily skilled artisan would have prioritized the development of inhibitors for better-known targets with demonstrated clinical results and validated pre-clinical tests. EAFOF ¶¶ 19, 21; *see supra* §III.A. An ordinarily skilled artisan would not have started with Kirin because it lacks such critical substantiation. EAFOF ¶ 22.

2. A Skilled Artisan Would Not Have Selected Kirin Example 5 as a Lead Compound Given the Kirin Inventors' Clearly Expressed Preference for Other Exemplified Compounds

Having selected Kirin as a primary reference, MSN then completely disregards the express teachings of the reference in its hindsight-driven selection of Example 5 as a lead compound. Kirin's list of "most preferred" compounds does not include a single malonamide, and specifically did not include Example 5. EAFOF ¶ 24; DTX-6 (Kirin) at 50. Moreover, while Kirin conducted in vivo testing in mice implanted with tumor cells for 23 of the 333 exemplified compounds, not a single malonamide was tested in vivo. EAFOF ¶¶ 27, 29; DTX-6 (Kirin) at 384-385, 389-393. Dr. Lepore's disregard of Kirin's express teachings is evidence of hindsight-based analysis.

Dr. Lepore's selection of Kirin Example 5 as a "lead compound" is at odds with Kirin's express teaching that other types of compounds were more preferred than malonamides. Kirin generally discloses millions of compounds and specifically exemplifies 333 compounds falling into five categories: thioureas (160 compounds), ureas (99 compounds), biurets (42 compounds), malonamides (31 compounds), and amide (one compound). EAFOF ¶¶ 22-24. As Dr. Lepore acknowledged, thioureas are the most common among Kirin's 333 exemplified compounds, whereas malonamides represent fewer than 10% of the exemplified compounds. EAFOF ¶ 23. Kirin's clear preference for compounds other than malonamides is further evidenced in its list of "particularly preferred" and "most preferred" compounds. Of the 101 "particularly preferred"

compounds, only eight are malonamides, while more than half are thioureas, and one-third are ureas. EAFOF ¶ 24; DTX-6 (Kirin) at 50. And not a single one of Kirin's five "most preferred" compounds is a malonamide, let alone Example 5. EAFOF ¶ 24. The "most preferred" compounds include three thioureas, one amide, and one urea. EAFOF ¶ 24; DTX-6 (Kirin) at 50. As Dr. MacMillan correctly observed, "a person of ordinary skill reading [Kirin] would see that the authors of this document designate most preferred compounds as being thioureas, ureas, and amides. But not biurets or malonamides." Tr. 684:3-9 (MacMillan); EAFOF ¶ 25. And, certainly not Example 5.

Dr. Lepore's selection of a malonamide as a lead compound also cannot be reconciled with the absence of any reported in vivo testing of malonamides in Kirin. As Dr. MacMillan explained, in vivo tests are more valuable than in vitro tests because animal models provide a much better approximation of how a compound will behave in humans. EAFOF ¶ 26. Kirin reports data from three in vivo tests in which tumor cells were implanted into mice. EAFOF ¶ 27; DTX-6 (Kirin) at 384-385, 389-393. Of the 23 Kirin compounds tested in at least one of the three in vivo tests, not one was a malonamide. EAFOF ¶ 27. The only data reported for any exemplified malonamide—including Example 5—resulted from a single in vitro pharmacological test that was performed on all 333 exemplified compounds. EAFOF ¶ 29. A skilled artisan would have understood Kirin to have selected the most promising compounds for in vivo testing. EAFOF ¶ 26. None of those 23 compounds were malonamides. The conclusion an ordinarily skilled artisan would have drawn is clear: the Kirin inventors did not view malonamides to be as promising as other exemplified compounds. EAFOF ¶ 28; DTX-6 (Kirin) at 50, 384-385, 389-393. Dr. Lepore's selection of Example 5 as a lead compound over the at least 23 other compounds that were clearly more highly valued by the Kirin inventors is yet further evidence of MSN's hindsight-based approach. *See*

Pfizer Inc. v. Mylan Pharms. Inc., 71 F. Supp. 3d 458, 471 (D. Del. 2014) (selection of a lead compound with only in vitro data "appears largely the result of hindsight"), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016).

3. Dr. Lepore's Rationale for Excluding Entire Classes of Compounds Preferred by Kirin is Not Persuasive

To circumvent Kirin's clear preference for thioureas, MSN and Dr. Lepore argue that an ordinarily skilled artisan would "deprioritize the thiourea compounds because of known toxicity concerns with these compounds." MSN Br. at 14. And they arbitrarily exclude from consideration two other categories of "most preferred" compounds identified in Kirin: ureas and amides. Both propositions are unsupported by the evidence.

First, a skilled artisan would not have disregarded an entire class of compounds such as thioureas without a more detailed analysis of individual compounds. As Dr. MacMillan explained, as "a person of ordinary skill, a medicinal chemist, you don't . . . take whole categories of molecules and just throw them out lock, stock and barrel." Tr. 694:13-25 (MacMillan); EAFOF ¶ 30. This is particularly so given that Kirin prioritized thioureas. EAFOF ¶ 24. Thioureas are the most common of Kirin's 333 exemplified compounds; half of the "particularly preferred" compounds; and 60% of the "most preferred compounds." EAFOF ¶ 24; DTX-6 (Kirin) at 50. As Dr. Lepore acknowledged, the three most potent compounds in Table 2 of Kirin are thioureas. EAFOF ¶ 29. Moreover, most in vivo testing was done on thioureas. EAFOF ¶ 27. Yet Dr. Lepore casts all this disclosure aside to categorically exclude thioureas from his lead compound analysis.

The alleged "toxicity" justification for Dr. Lepore's exclusion of thioureas is fundamentally flawed; it is simply not true that a skilled artisan would have disregarded all thioureas as potentially toxic. The Kirin inventors certainly did not. EAFOF ¶ 24. As Dr.

MacMillan explained, Onderwater 1998, upon which Dr. Lepore relies for his toxicity point, shows that in September 2003, thiourea compounds were being used in human patients. EAFOF ¶ 32; DTX-18 (Onderwater 1998) at 2. A thiourea compound known as methimazole was approved to treat Graves' disease, and another thiourea compound called trovirdine was in clinical development for treatment of AIDS. EAFOF ¶ 32. Moreover, Dr. Lepore's comparison of a diphenylthiourea shown in the Onderwater reference to Kirin Example 1 is inapt. EAFOF ¶ 33. As Dr. MacMillan explained, the benzene ring in the diphenylthiourea simply does not correlate to the carbonyl in Kirin Example 1 and would not have led a skilled artisan to disregard all of the thioureas reported in Kirin as potentially toxic. EAFOF ¶¶ 31, 33.

Second, Dr. Lepore's disregard of ureas and amides is similarly without basis. Urea and amide compounds were among Kirin's "most preferred" and were tested in the most important in vivo studies. EAFOF ¶¶ 24, 27. Moreover, Kirin discloses urea compounds that are more potent than Example 5 and among the most potent of all the disclosed compounds. EAFOF ¶¶ 29, 34; DTX-6 (Kirin) at 385-389. And Dr. Lepore admitted that he did not identify any toxicity issues with ureas or amides or offer an opinion that they were metabolically unstable. EAFOF ¶ 34. As to ureas, Dr. Lepore dismissed them categorically on the ground that they could not form irreversible inhibitors. Tr. 438:25-439:11 (Lepore). But as Dr. MacMillan explained, even if development of an irreversible inhibitor were a goal (which is contradicted by the evidence, *see infra* § III.C.1), a skilled artisan could have in fact modified the ureas exemplified in Kirin to be potential irreversible inhibitors. EAFOF ¶ 34. And Dr. Lepore did not present any reason at all as to why a skilled artisan would have disregarded the amide that is included in Kirin's list of "most preferred" compounds, in favor of Example 5. EAFOF ¶¶ 24, 34; DTX6 (Kirin) at 50.

Finally, Dr. Lepore's approach to the selection of a lead compound is internally inconsistent. On the one hand, Dr. Lepore categorically dismissed Kirin's preferred thiourea compounds on the ground that they raised potential toxicity concerns. *See* Tr. 437:12-20, 489:17-490:5 (Lepore). On the other hand, despite acknowledging that malonamides can be metabolically unstable (and therefore prone to toxicity), Dr. Lepore selected Example 5 as a lead compound. *See* Tr. 487:14-488:14 (Lepore). As Dr. MacMillan observed: "So, it's almost saying, I'm going to throw out a whole class of compounds to focus on a molecule that has a problem." Tr. 703:1-11 (MacMillan); *see* EAFOF ¶¶ 31, 35. That simply doesn't make sense and further demonstrates MSN's hindsight-based approach.

4. A Skilled Artisan Would Not Have Selected Example 5 Over Other More Potent Malonamides Disclosed in Kirin

MSN's hindsight-driven approach is further evident in Dr. Lepore's selection of Example 5 over Example 269, another malonamide that is clearly more potent. As acknowledged by MSN and Dr. Lepore, Example 269 was more potent than Example 5 and had other properties Dr. Lepore viewed as favorable. *See* MSN Br. at 15; EAFOF ¶ 37; *Daiichi*, 619 F.3d at 1354 ("Potent and promising activity in the prior art trumps mere structural relationships."). In order to dismiss Example 269 of Kirin as a lead compound, Dr. Lepore resorted to the so-called Lipinski's rules. But as Dr. MacMillan explained, a skilled artisan would not have ruled out Example 269 as a lead compound based on Lipinski's rules. EAFOF ¶ 41.

Lipinski's rules provide a general set of criteria that can be used to alert medicinal chemists to potential bioavailability issues. EAFOF ¶ 38. Lipinski's rules are guidelines, not hard and fast rules. EAFOF ¶ 38. In fact, there are many FDA-approved drugs that do not satisfy one or more of the criteria set forth in Lipinski's rules. EAFOF ¶ 38. For example, one of Lipinski's rules suggests that molecular weight should not be above 500 grams per mole. EAFOF ¶ 38. However,

in 2003, there were FDA-approved drugs, including cancer therapies, as well as compounds (including TKIs) being tested in the clinic that had molecular weights above 500 grams per mole. EAFOF ¶ 38.

Moreover, as Dr. Lepore and MSN tacitly admit, Example 269 does not violate Lipinski's rules. MSN Br. at 15 n.2. To violate Lipinski's rules, a compound must fail two or more of Lipinski's four criteria. EAFOF ¶ 39. Example 269 meets all the Lipinski criteria except molecular weight, and, as Dr. MacMillan explained, its molecular weight "would not raise a flag." Tr. 700:4-21 (MacMillan); EAFOF ¶ 39. Although Dr. Lepore observed that Example 269 is at the "borderline" of the Lipinski range for Log P, Tr. 438:6-24 (Lepore), it is in the range and thus satisfies that criterion. EAFOF ¶ 39. In short, an ordinarily skilled artisan would not have excluded Example 269 for a violation of Lipinski's rules for the simple reason that there is no violation. EAFOF ¶ 41. Nor would the differences in molecular weights between Examples 269 and 5 have dissuaded a POSA from prioritizing the more potent Example 269. EAFOF ¶ 40.

C. A Skilled Artisan Would Not Have Been Motivated to Modify Example 5 By Adding a Cyclopropyl Group to the Malonamide

MSN has failed to present clear and convincing evidence that an ordinarily skilled artisan would be motivated to modify Kirin Example 5 by adding a cyclopropyl group between the two carbonyls. As an initial matter, Dr. Lepore's assertion that a skilled artisan would have been motivated to make an irreversible inhibitor in September 2003 is at odds with the testimony of the parties' clinical experts, Dr. George and Dr. Mega. EAFOF ¶ 42. Moreover, Dr. Lepore's hindsight-driven focus on the addition of a cyclopropyl group to the malonamide ignores the substantial concerns that a skilled artisan would have had about such a significant modification with a potentially unstable substituent, including the potential impact on toxicity and potency. EAFOF ¶¶ 44-48. Notably, Dr. Lepore did not identify at trial a single prior art reference

disclosing a malonamide substituted with a cyclopropyl group. EAFOF ¶¶ 44, 47. A skilled artisan would have had no suggestion in the prior art, and therefore no motivation, to make such a modification.

1. A Skilled Artisan Would Not Have Been Motivated to Develop an Irreversible c-Met Inhibitor

In an effort to support its theory that a skilled artisan would have been motivated to modify Example 5 by adding a cyclopropyl group to the malonamide, MSN asserts that a skilled artisan would have been motivated to pursue an irreversible inhibitor and that "there is no dispute about the desirability of an irreversible inhibitor." MSN Br. at 10. The logic of this argument is hard to follow, given that cabozantinib is, in fact, a reversible inhibitor. But in any event, MSN's premise is incorrect. Both Dr. George and Dr. MacMillan testified that a skilled artisan would not have been motivated to pursue an irreversible inhibitor in September 2003. EAFOF ¶ 42. Dr. George explained that while an irreversible inhibitor may have the benefit of irreversibly blocking a target in a cancerous tumor, irreversibility is not beneficial if the same target is, for example, important to facilitating blood supply to the body or maintenance of skin. EAFOF ¶ 42. Dr. MacMillan testified similarly that he disagreed with Dr. Lepore that a skilled artisan would have sought to develop an irreversible inhibitor, and described the "very, very significant" potential for toxicity. Tr. 715:19-716:5 (MacMillan); EAFOF ¶ 42. Dr. MacMillan also pointed out that one of the irreversible inhibitors cited by Dr. Lepore, CI-1033, turned out to be toxic. EAFOF ¶ 42. Although MSN misleadingly characterizes Dr. MacMillan's testimony on the subject of irreversible inhibitors by quoting the single word "wonderful" (MSN Br. at 10), Dr. MacMillan in fact testified on cross examination that while an ordinarily skilled artisan understood the potential benefits of an irreversible inhibitor, they would "at the same time [have] understood the pitfalls and toxicity aspects" of an irreversible inhibitor and that "it's very much a risk-reward system"

and a "far more difficult thing . . . to pull off." Tr. 731:9-20 (MacMillan); EAFOF ¶ 42. Indeed, the risks associated with irreversible inhibitors have resulted in a decision finding that in the early 2000s "there was widespread industry aversion to irreversible inhibitors for drug products." *Onyx Therapeutics, Inc. v. Cipla Ltd.*, C.A. No. 16-988-LPS, 2020 WL 2214443, at *14 (D. Del. May 4, 2020), *aff'd* 839 F. App'x 545 (Fed. Cir. 2021).

MSN's own experts provided little support for Dr. Lepore's theory that a skilled artisan would have been motivated to make an irreversible inhibitor. Dr. Lepore is not an oncologist and, for example, admitted that he was relying upon Dr. Mega to determine what a skilled artisan would target in the development of a cancer treatment. Tr. 463:16-464:8 (Lepore). Dr. Mega merely stated that a skilled artisan could have pursued either an irreversible or reversible inhibitor without expressing an opinion on the merit of either pursuit. EAFOF ¶ 42. The record is thus devoid of any clinical expert opining that a skilled artisan would have been motivated to modify an existing c-Met inhibitor to make it irreversible. Moreover, the Fry paper relied upon by MSN (MSN Br. at 10) does not support the assertion that a skilled artisan would have sought to develop an irreversible c-Met inhibitor in September 2003. EAFOF ¶ 43; DTX-30 (Fry). Fry describes the development of an irreversible inhibitor of EGFR and ERBB2, not c-Met. EAFOF ¶ 43. As Dr. MacMillan explained, in September 2003, researchers could better predict potential impact of irreversibility in the context of inhibition of EGFR and ERBB2 because they had structural information about the binding pocket for those tyrosine kinases. EAFOF ¶ 43. In contrast, much less was known about the c-Met kinase in September 2003. EAFOF ¶ 43. Unlike the more studied tyrosine kinases, such as EGFR and ERBB2, no structural information was available for c-Met. EAFOF ¶¶ 19, 43; *see supra* § III.A.

2. A Skilled Artisan Would Not Have Been Motivated to Add a Cyclopropyl Group to Kirin Example 5

Although chemical compounds are often depicted in two dimensions, tyrosine kinases and TKIs exist in three dimensions. *See supra* § II.B; *see also* EAFOF ¶ 46. As Dr. MacMillan analogized, the tyrosine kinase is a lock and the TKI is a key. EAFOF ¶ 46. For the TKI to function well, you need a "snug fit" between the grooves of the lock and key. Tr. 669:13-20 (MacMillan); EAFOF ¶ 46. One of the "essential paradigms" of molecular chemistry is that even small changes to a compound can cause large effects. Tr. 667:19-25 (MacMillan); EAFOF ¶¶ 46, 50.

A cyclopropyl group is a small three-membered ring of carbon atoms that when added to a molecule would change the three-dimensional structure of the molecule. EAFOF ¶¶ 44, 46. Given the ring configuration, the carbon-to-carbon bonds in a cyclopropyl group are not linear but are folded and bent. EAFOF ¶ 45. This results in "ring strain," such that the carbon-to-carbon bonds of the cyclopropyl ring are susceptible to breaking.[7] EAFOF ¶ 45. Given these properties, an ordinarily skilled artisan would have had substantial concerns about adding a cyclopropyl group between the carbonyls in Example 5.

First, the addition of a cyclopropyl group is a significant change that would not only have altered the three-dimensional shape of Example 5 but could have unpredictably altered the compound's functionality. EAFOF ¶ 46. As Dr. MacMillan explained with reference to the lock and key analogy, if the grooves on the key are changed (here, by adding a cyclopropyl group to Example 5), the ability to interact with the lock (here, c-Met) may also change, and a skilled artisan

[7] At trial, Dr. MacMillan explained the difference between normal linear bonds and the folded bonds in a cyclopropyl group with reference to a piece of dry spaghetti. Linear bonds are strong; if you pull straight on each end of a piece of dry spaghetti, it is unlikely to break. Folded bonds are strained; if you put your thumb in the middle and slowly start to bend the piece of spaghetti, it will snap. Tr. 706:13-707:13 (MacMillan).

would not know whether the molecule will inhibit c-Met or not. EAFOF ¶ 46. The unpredictability of adding any group at any position (including, but certainly not limited to a cyclopropyl group at that particular position on Example 5) would have been particularly acute because in September 2003, skilled artisans did not have structural information for c-Met (i.e., the shape of the "lock" was not known). EAFOF ¶ 46. As a result, one could not have predicted how changing Example 5 (i.e., the "key") would have impacted the compound's ability to inhibit c-Met. EAFOF ¶ 46.

In an effort to address the substantial uncertainty that a skilled artisan would have had about the modification proposed by Dr. Lepore, MSN resorts to prior art describing cyclopropyl-containing compounds known as "illudins." MSN Br. at 20 (citing DTX-25 (McMorris) and DTX-27 (Kelner)). MSN contends that, because illudins were irreversible inhibitors, a skilled artisan would reasonably have expected the modified Example 5 to irreversibly inhibit c-Met. *Id.* However, even MSN concedes that a geminal cyclopropyl analog of Example 5 would only irreversibly inhibit c-Met if c-Met had a "properly located nucleophile," which MSN refers to as a "molecular hook." MSN Br. at 20. And of course, whether or not c-Met had such a hook was unknown in September 2003. EAFOF ¶¶ 19, 43, 46. Moreover, Dr. MacMillan explained that illudins are a class of molecules that interact with DNA, not tyrosine kinases, let alone c-Met. EAFOF ¶ 47. An ordinarily skilled artisan would thus have found literature regarding illudins to be "simply irrelevant to the analysis of Compound 5 and cabozantinib." Tr. 711:5-24 (MacMillan); EAFOF ¶ 47.

Second, a skilled artisan would have had concerns that adding a cyclopropyl group between the carbonyl groups of Example 5 could have resulted in increased toxicity. EAFOF ¶ 48. Contrary to MSN's assertion that a skilled artisan would have been drawn to cyclopropyl groups based on the Salaün reference (MSN Br. at 21), Salaün confirms that the position between the two

carbonyls on Example 5 is extremely reactive for a cyclopropyl. EAFOF ¶ 48; *see also* DTX-28 (Salaün). Adding a cyclopropyl group to that position would result in an extremely reactive cyclopropyl group and create ring strain in the molecule, giving a skilled artisan "significant concerns about reactivity which leads to toxicity." Tr. 672:22-673:6 (MacMillan); EAFOF ¶ 48; *see also* DTX-28 (Salaün).

Third, Kirin itself suggests that adding a substituent to the position between the carbonyl groups in Example 5, could reduce the potency by 3.3 to 9.1 times. EAFOF ¶ 49; DTX-6 (Kirin) at 385-389; PDX-5.33. Introducing a second substituent in related compounds was shown to reduce potency by even more, 3.75 to 12.8 times. EAFOF ¶ 49; DTX-6 (Kirin) at 385-389; PDX-5.33. A skilled artisan considering Kirin would not, therefore, have been motivated to add a substituent between the carbonyl groups in the malonamide group in Example 5. EAFOF ¶¶ 48, 49.

D. A Skilled Artisan Would Not Have Had a Reasonable Expectation of Success

MSN failed to present clear convincing evidence that an ordinarily skilled artisan would have had a reasonable expectation of success in obtaining a compound with the properties of cabozantinib after modifying Kirin Example 5 by adding a cyclopropyl group. *See, e.g.*, *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) ("From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing.").

First, a skilled artisan would have had no reasonable expectation that the resulting compound would be potent and non-toxic. As a general matter, the drug development process for new cancer therapeutics is an unpredictable, arduous process, in which many compounds are attempted to be developed without success. EAFOF ¶ 50 n.4. Moreover, medicinal chemistry is unpredictable, and it is "very difficult to know what's going to happen" when one or more substitutions introduce new groups into a compound. Tr. 718:13-720:15 (MacMillan); EAFOF

¶ 50. The unpredictability is even more acute here because the structure of the c-Met tyrosine kinase was not known. EAFOF ¶ 50. Introducing a cyclopropyl group to Example 5, particularly between the carbonyl groups, would have given a skilled artisan concern about reactivity, which could have resulted in toxicity. Tr. 719:10-20 (MacMillan) ("As we discussed, we – a person of ordinary skill would have significant concerns with reactivity of that as this bending phenomenon."); EAFOF ¶ 48. Introducing a cyclopropyl group in that position would have also created concerns about reduced potency, i.e., "the Kirin reference itself told us that when you introduce groups at that position of a malonamide, that the potency would actually diminish." Tr. 719:10-25 (MacMillan); EAFOF ¶ 49; PDX-5.33.

Second, a skilled artisan would have had no reasonable expectation that Example 5, or any modified Example 5, would have resulted in a spectrum-selective tyrosine kinase inhibitor such as cabozantinib. *See In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) ("[A] compound and all of its properties are inseparable and must be considered in the determination of obviousness."), *cert. denied*, 111 S. Ct. 1682 (1991). A skilled artisan would have had no idea based on information in Kirin about spectrum selectivity, because "the Kirin reference itself, only spoke to c-Met data. It didn't tell you anything about any other kind of tyrosine kinases" and at the time it was "really difficult to predict the inhibition that would be acquired." Tr. 720:1-8 (MacMillan); EAFOF ¶ 51.

Third, even if one's objective were to develop an irreversible inhibitor, a skilled artisan would not have reasonably expected that adding a cyclopropyl group to Example 5 would have resulted in an irreversible inhibitor. EAFOF ¶ 52. Dr. Lepore admitted as much when he testified that: "It was a possibility that it could be reversible or irreversible depending upon the enzyme . . . [t]hat was true before the crystal structure of the molecule was available and one didn't know for sure." Tr. 463:2-463:8 (Lepore); EAFOF ¶ 52. And of course, in fact, cabozantinib is not an

irreversible inhibitor. EAFOF ¶ 52. This confirms the unpredictability of the substitution suggested by Dr. Lepore. Tr. 806:9-23 (Mega) (confirming that an ordinarily skilled artisan looking for an irreversible inhibitor would not have been led to cabozantinib); EAFOF ¶ 52.

E. Objective Evidence Further Demonstrates Non-Obviousness

Objective evidence further confirms that claim 5 of the '473 patent would not have been obvious. Cabozantinib, the active ingredient of Exelixis' CABOMETYX® product, has a unique and unexpected tyrosine kinase inhibition profile that has resulted in significant clinical success in the treatment of RCC, HCC, and certain thyroid cancers.[8] EAFOF ¶¶ 8, 53, 59. CABOMETYX® has also been a tremendous commercial success. Given that the active ingredient of CABOMETYX® is cabozantinib, a nexus exists between claim 5 of the '473 patent and its commercial embodiment, CABOMETYX®. EAFOF ¶ 53; *see also Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020) ("Nexus is appropriately presumed in this case where the court concluded that the claims are directed to the active ingredient in Enbrel® and its method of manufacture."), *cert. denied*, 141 S. Ct. 2623 (2021).

1. Cabozantinib Fulfilled a Long-Felt, Unmet Need for Improved Cancer Treatment

As of September 2003, there was a significant unmet need for improved cancer treatments. EAFOF ¶ 55. The most common cancer treatments—surgery, chemotherapy, and radiation—had major shortcomings (*see supra* at § III.A), and there was a significant need for improved treatments for RCC, HCC and thyroid cancer. EAFOF ¶¶ 14, 55-57. CABOMETYX® has been approved for treatment of RCC, HCC, and certain thyroid cancers, and, as even as Dr. Mega admits, extended

[8] In 2021, in the United States, there were an estimated 76,000 diagnoses of kidney cancer and 13,000 deaths, an estimated 42,000 diagnoses of HCC and 30,000 deaths, and an estimated 44,000 diagnoses of thyroid cancer and 2,000 deaths. Tr. 542:10-544:6 (George); EAFOF ¶ 8 n.1.

patient lives. EAFOF ¶¶ 8, 57. Cabozantinib has thus fulfilled the long-felt unmet need for improved therapy. EAFOF ¶¶ 55-57.

Cabozantinib has been particularly effective in RCC patients who have failed prior therapies. EAFOF ¶¶ 56. As Dr. George explained, cancer therapies generally lose their effectiveness over time, and new therapies are needed to fill the void when prior treatments fail. EAFOF ¶ 56. Cabozantinib has done just that. EAFOF ¶¶ 56-58. For example, Exelixis' Phase III METEOR Study demonstrated that, when compared to the then standard of care second-line treatment everolimus, cabozantinib delayed disease progression and improved overall survival for RCC patients. EAFOF ¶ 57; PTX-647 (METEOR Study). On the basis of these significant results, CABOMETYX® was approved as a second-line therapy for the treatment of RCC. EAFOF ¶¶ 57, 58. CABOMETYX® was later approved as a first-line therapy after a clinical trial demonstrating significant clinical benefit in progression-free survival over sunitinib, the long-standing standard-of-care first-line treatment for RCC patients. EAFOF ¶ 57; PTX-505 (CABOSUN Study) at 5. The National Comprehensive Cancer Center's practice guidelines recognize cabozantinib as a preferred treatment for kidney cancer in several settings, including as a part of the preferred regimens for first-line therapy and subsequent therapy. EAFOF ¶ 57; PTX-648 (NCCN Guidelines) at 14-15.

The therapeutic effectiveness of CABOMETYX® is tied to cabozantinib's unique inhibition profile, which provides a difference-in-kind improvement over other treatments. EAFOF ¶¶ 53, 57. As Dr. George explained, cabozantinib "is doing something that no other drug in the field is doing in the refractory setting" while also showing "clear superiority" in front-line setting against drugs like sunitinib. Tr. 576:16-577:9 (George); EAFOF ¶ 57. It has the ability to extend patients' lives while maintaining quality of life. EAFOF ¶ 57.

That other drugs have been approved for the treatment of RCC, HCC and thyroid cancer does not—as MSN contends (MSN Br. at 22)—negate the existence of a long-felt, unmet need for improved therapies. As an initial matter, courts "look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). It is undisputed that there were no targeted therapies approved to treat RCC, HCC or thyroid cancer in September 2003. EAFOF ¶ 55. Moreover, the existence of competing drugs, particularly in a setting where drugs often lose efficacy, does not negate a long-felt need. *See, e.g.*, *Pfizer,* 71 F. Supp. 3d at 475 ("[E]ven with the competing drugs available, sunitinib malate satisfied a long-felt need in the treatment of these cancers."). This is particularly so with cabozantinib, which demonstrated improvement over earlier-approved therapies such as everolimus and sunitinib. *See supra* § III.E.1.

Similarly misguided is MSN's argument that cabozantinib has not satisfied a long and unmet need because it "only fills a need for improved therapy options . . . 'in part.'" MSN Br. at 22. MSN has cited no authority that requires Exelixis to demonstrate that cabozantinib fully satisfied the need for improved treatments for RCC, HCC, and thyroid cancer. In fact, this court has found the opposite. *See, e.g.*, *UCB*, 201 F. Supp. 3d at 538 (finding that treatment for epilepsy met long-felt need because even though it did not work for all patients, it had beneficial properties lacking in other available treatments). Because cabozantinib is an effective, life-extending treatment for multiple patient populations suffering from challenging, and sometimes fatal, cancers, it has satisfied a long-felt and unmet need.

2. Others Have Failed to Develop Safe and Effective Targeted Cancer Treatments

Exelixis also demonstrated the failure of others, which further supports the non-obviousness of the claimed cabozantinib. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569,

1578-79 (Fed. Cir. 1991) (nonobviousness is suggested by the failure of others to find a solution to the problem which the treatment purports to solve.). As Dr. George testified, cabozantinib "can work even in the setting where other drugs have failed." Tr. 577:19-25 (George); EAFOF ¶ 56.

Moreover, Exelixis need not show that others "failed to synthesize the compound of claim 5 of the '473 patent," as MSN incorrectly suggests. *See* MSN Br. at 23. "[I]t is not just the failure of others to identify the exact product claimed by the patents that is relevant." *Allergan, Inc. v. Teva Pharms. USA, Inc.*, No. 2:15-CV-1455-WCB, 2017 WL 1319555, at *2 (E.D. Tex. Apr. 10, 2017), *aff'd* 742 F. App'x 511 (Fed. Cir. 2018). The fact that others were going in different ways is strong evidence of non-obviousness. *Id.* Here, the clinical experts agreed that there have been many failures in the development of cancer therapeutics. EAFOF ¶¶ 50 n.4, 58. Moreover, even within the context of c-Met inhibitors, Dr. MacMillan and Dr. George testified at trial that none of the Kirin compounds advanced to clinical development, suggesting that these compounds were failures as well. EAFOF ¶ 58.

3. Cabozantinib Unexpectedly Has a Unique Spectrum-Selective Inhibition Profile

Cabozantinib, with its unique spectrum-selective profile, achieved unexpected clinical results. The clinical efficacy of second- and third-line treatments were unknown because no such treatments existed. EAFOF ¶ 58. Not only did cabozantinib work in patients who had been treated with other tyrosine kinase inhibitors, but cabozantinib worked when these other drugs stopped working. EAFOF ¶ 58.

Cabozantinib's clinical success is due to its inhibition of a unique and unexpectedly broad spectrum of tyrosine kinase targets—MET, VEGF-receptor 1, 2 and 3, AXL, RET, ROS1, TYR03, MER, KIT, TRKB, FLT-3 and TIE-2. EAFOF ¶¶ 10, 53; PTX-343 (CABOMETYX® Label) at 28. As of 2003, and even now, there are no known tyrosine kinase inhibitors with the same

inhibition profile as cabozantinib. EAFOF ¶ 51. This unique inhibition profile was the "secret sauce" that resulted in the clinical benefit. EAFOF ¶ 53. In 2003, an ordinarily skilled artisan would not have expected this profile, let alone the clinical results. EAFOF ¶¶ 51, 58.

MSN's contention that Exelixis has failed to establish unexpected results because Dr. George did not conduct any comparison with Kirin Example 5 (MSN Br. at 24) is incorrect. It is undisputed that no Kirin compound has ever been approved for human use. EAFOF ¶ 58. Therefore, there is a significant clinical benefit associated with cabozantinib that is not associated with Kirin Example 5 or any other compound disclosed in Kirin. EAFOF ¶ 58.

4. CABOMETYX® is a Commercial Success

There can be no doubt that CABOMETYX® has been a tremendous commercial success. EAFOF ¶¶ 59-60. As Exelixis' expert Michael Tate testified: CABOMETYX ® made over $1 billion in net product revenue in 2021 and over $3 billion in net product revenue since its launch. EAFOF ¶ 59; PTX-896. By the second quarter of 2021, at least 34,000 patients had been treated with CABOMETYX®. EAFOF ¶ 59; PTX-364. MSN's critiques that Mr. Tate did not make "comparisons to other products," did not evaluate the "commercialization costs to bring the product to market," and relied on "uninformative market shares" (MSN Br. at 24) do not rebut commercial success. *See, e.g.*, *UCB, Inc.*, 201 F. Supp. 3d at 522-23 (finding commercial success where drug product including claimed compound generated significant sales, totaling $1.67 billion in the U.S. since its launch). Indeed, MSN did not rebut Exelixis' claim of nexus between claim 5 and CABOMETYX®. EAFOF ¶ 54.

IV. CONCLUSION

For the reasons above, Exelixis respectfully requests that the Court determine that claim 5 of the '473 patent is not invalid and find that making, using, offering to sell, or selling in the United States, or importing into the United States MSN's proposed 20 mg, 40 mg, and 60 mg generic

cabozantinib tablets ("MSN's Tablets") will literally infringe claim 5 of the '473 patent and, therefore, that the submission of MSN's ANDA infringes that claim under 35 U.S.C. § 271(e)(2)(A) and that upon FDA approval MSN will infringe that claim under 35 U.S.C. § 271(a). Exelixis further requests that the Court enter an order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of MSN's ANDA shall be a date which is not earlier than the latest expiration date of the Patents-in-Suit, including any extensions and/or additional periods of exclusivity to which Exelixis is or becomes entitled, and an order permanently enjoining MSN, its affiliates, subsidiaries, and each of its officers, agents, servants and employees and those acting in privity or concert with them, from making, using, offering to sell, or selling in the United States, or importing into the United States MSN's Tablets until after the latest expiration date of the Patents-in-Suit, including any extensions and/or additional periods of exclusivity to which Exelixis is or becomes entitled.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Anthony D. Raucci

Jack B. Blumenfeld (#1014)
Anthony D. Raucci (#5948)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@morrisnichols.com
araucci@morrisnichols.com

Attorneys for Plaintiff Exelixis, Inc.

OF COUNSEL:

William F. Lee
Lisa J. Pirozzolo
Emily R. Whelan
Kevin S. Prussia
Timothy A. Cook
WILMER CUTLER PICKERING
HALE AND DORR LLP
60 State Street
Boston, MA 02109
(617) 526-6000

Amy K. Wigmore
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Avenue, NW
Washington, DC 20006
(202) 663-6000

July 22, 2022

CERTIFICATE OF SERVICE

I hereby certify that on July 22, 2022, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on July 22, 2022, upon the following in the manner indicated:

Dominick T. Gattuso, Esquire — *VIA ELECTRONIC MAIL*
HEYMAN ENERIO GATTUSO & HIRZEL LLP
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
Attorneys for Defendants MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.

George C. Lombardi, Esquire — *VIA ELECTRONIC MAIL*
Bryce A. Cooper, Esquire
Kevin J. Boyle, Esquire
Kurt A. Mathas, Esquire
WINSTON & STRAWN LLP
35 West Wacker Drive,
Chicago, IL 60601-9703
Attorneys for Defendants MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.

Noorossadat Torabi, Esquire — *VIA ELECTRONIC MAIL*
WINSTON & STRAWN LLP
101 California Street, 35th Floor
San Francisco, CA 94111-5840
Attorneys for Defendants MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc.

/s/ Anthony D. Raucci

Anthony D. Raucci (#5948)